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(54) **Compositions containing aldose reductase inhibitors for the treatment of ulcers.**

(57) A therapeutic preparation for the treatment of dermal, labial, intra-oral and gastro-intestinal tract ulcers, corrosive wounds, bed sores, burns, frost-bite and scleroderma contains as a primary ingredient a compound having an aldose reductase inhibitory activity and which can accelerate dermal metabolism. Preferred compounds are optically active hydantoin derivatives.

EP 0 437 025 A2

THERAPEUTIC COMPOSITIONS FOR TREATING ULCERS

This invention relates to a therapeutic composition for the treatment of ulcers and containing an aldose reductase as a primary component. The compositions may be administered externally for the treatment of labial and dermal ulcers, corrosive wounds, bed sores (decubitus), burns, frostbite and scleroderma, and administered internally for the treatment of intra-oral and gastro-intestinal tract ulcers.

In recent years, it has been found that one of the causes of cataract, retinitis and various nervous disorders induced by diabetes is an intracellular accumulation of sorbitol formed by way of the polyol pathway, and attention has been paid to various aldose reductase inhibitory substances, because enzymatic inhibition of the exchange between aldose and polyol reduces the production or accumulation of sorbitol.

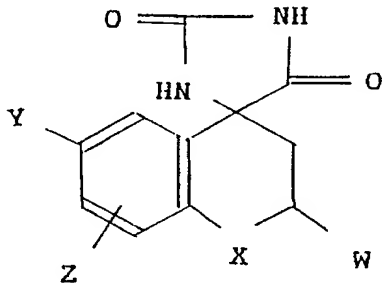
The applicant has already filed patent applications to patent per se the compounds used in this invention (see Japanese Patent Kokai Publication No 61(1986)-200991 and US Patent No 4,861,792).

Hitherto, many aldose reductase inhibitors have been studied for treating diabetic complications (see US Patent No 4,900,739). However, it has not previously been known that aldose reductase inhibition systems take part in the promotion of tissue metabolism, and that they also have an effect upon inhibiting ulceration.

According to one aspect of the present invention, the aldose reductase inhibitor includes a compound having an aldose reductase inhibitory activity, such as one of those available in the form of pharmaceeutical preparations, for instance, Sorbinil (CAS 68367-52-2), Epalrestat (CAS 82159-09-9) and Ponalrestat (CAS 72702-95-5) which are now commercialized or under development. However, preference is given to hydantoin compounds.

According to another aspect of the present invention, there is provided a therapeutic composition which contains an aldose reductase inhibitory substance, especially a class of optically active hydantoin derivatives, and which, whether of a type for internal administration or for external administration, is well-absorbed after administration by ulcerated regions.

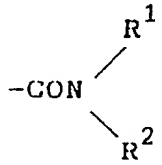
The hydantoin compounds used in this invention include an optically active class of hydantoin derivatives expressed by the following general formula:



wherein:

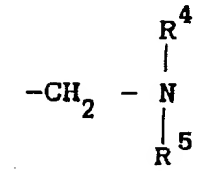
W stands for a halogenomethyl group, a 1H-tetrazol-5-yl group, a -COOR group in which R is a hydrogen atom, an alkyl group or a $-(CH_2CH_2O)_nCH_3$ group in which n is an integer of 1-113,or a substituted phenyl group;

a



group in which R^1 and R^2, which may be identical with or different from each other, each represents a hydrogen atom, an alkyl group, a $-(CH_2CH_2O)_nCH_3$ group in which n is an integer of 1-11, or a substituted

phenyl group, or alternatively R^1 and R^2 may form a 5- or 6-membered heterocyclic ring together with a nitrogen atom or other nitrogen atom or oxygen atom; a $-CH_2OR^3$ group in which R^3 is a hydrogen atom or an alkyl group; or a



group wherein R^4 and R^5, which may be identical with or different from each other, each represents a hydrogen atom or an alkyl group,
X stands for an oxygen or sulfur atom; and
Y and Z, which may be identical with or different from each other, each stands for a hydrogen or halogen atom, or alkyl, alkoxy or alkylmercapto group. Particular mention is made of d-6-fluoro-2,3-dihydro-2',5'-dioxo-spiro [4H-1-benzopyran-4,4'-imidazolidine]-2-carboxyamide, d-2-chloromethyl-6-fluoro-2,3-dihydro-spiro [4H-1-benzopyran-4,4'-imidazolidine]-2',5'-dione and d-2-bromomethyl-6-fluoro-2,3-dihydro-spiro [4H-1-benzopyran-4,4'-imidazolidine]-2',5'-dione. If desired, the hydantoin derivatives may be provided in the form of a composition to which stabilizers, absorption accelerators have been added. Examples of the carriers that may be used are carboxylmethylcellulose, polyvinyl pyrrolidone and cyclodextrin.

The therapeutic compositions according to this invention activate tissue metabolism and so are efficacious against all aspects of exhaustion tissue necroses including intra-oral and dermal ulcers.

The present preparations are particularly efficacious against one of the aspects of exhaustion tissue necroses,
cuticular ulcers such as senile and traumatic decubiti, to say nothing of diabetic decubitus. Besides, they are useful for treating burns, frostbite and scleroderma.

The present preparations are also administrable to labial, gastrointestinal tract and defective tissue ulcers.

The present invention will now be illustrated more specifically with reference to pharmacological Tests and non-limiting Examples.

EXAMPLES

Preparation Examples

Three hydantoin derivatives, i.e., d-6-fluoro-2,3-dihydro-2',5'-dioxo-spiro [4H-1-benzopyran-4,4'-imidazolidine]-2-carboxyamide (hereinafter called Compound A), d-2-chloromethyl-6-fluoro-2,3-dihydro-spiro [4H-1-benzopyran-4,4'-imidazolidine]-2',5'-dione hereinafter called Compound B) and d-2-bromomethyl-6-fluoro-2,3-dihydro-spiro [4H-1-benzopyran-4,4'-imidazolidine]-2',5'-dione (hereinafter called Compound C) are used to obtain the following forms of preparation: (a) ointment, (b) liquid for external administration, (c) cream, (d) suppository and (e) tablet.

(a) Ointment

Compound A is dispersed in a ten-fold amount of cyclodextrin	**100 g**
25 % hydrolyzed lanolin	**600 g**
White petrolatum	**300 g**
	Total: 1000 g

The above-mentioned components are mixed together to prepare an ointment containing 10 mg of Compound A per 1 g.

(b) Liquid for external administration (Emulsifiable lotion)

Compound B	1.0 g
Carboxymethylcellulose	0.5 g
Stearyl alcohol	2.5 g
Liquid paraffin	20.0 g
Sodium lauryl sulfate	1.0 g
Propylene glycol	17.0 g
Methyl p-hydroxybenzoate	0.025 g
Propyl p-hydroxybenzoate	0.015 g
Purified water	balance
	Total: 100.0 ml

Liquid paraffin is added to stearyl alcohol dissolved on a water bath. Afterwards, the solution is heated to 70 °C (an oil layer). The remaining components, on the other hand, are added to hot water, which is then held at 70 °C to prepare a water layer.

The water layer is added to the oil layer, and the resulting solution is cooled down to 45 °C under agitation and cooled off, thereby obtaining an emulsifiable lotion.

(c) Cream

(Layer A)	
Polyoxyl 40 stearate	50 g
Glycerin fatty acid ester	140 g
Tallow fatty acid glyceride	70 g
Cetanol	60 g
Butyl p-hydroxybenzoate	1 g
(Layer B)	
Compound C	10 g
Propylene glycol	50 g
Methyl p-hydroxybenzoate	1 g
3 % aqueous solution of albumin	100 g
Purified water	balance
Total (A+B):	1000 g

The layers A and B are separately heated to 70-80°C. While the layer A is stirred, the layer B is gradually added thereto. The product is stirred at 45°C under reduced pressure, and then cooled off to obtain a desired cream.

(d) Suppository

Compound A	100 mg
Cacao butter	1600 mg
	1700 mg per suppository

Compound A is dispersed in a cacao butter (higher fatty acid glyceride) melt that is an oil and fat base, and then formed in conventional manner to obtain suppositories. (e) Tablet

Compound A	50 g
Sodium citrate	25 g
Arginine	10 g
Polyvinyl pyrrolidone	10 g
Magnesium stearate	5 g

In conventional manner the above-mentioned components are tableted to prepare 1000 tablets for oral administration, each containing 50 mg of the active component.

Pharmacological Test Example 1

Effect on Inhibiting Ulcer Induced by Water Immersion Stress

After 24-hour fasting, S.D. masculine rats weighing 250-270 g were immersed to their breasts in a water tank maintained at 23 1 to load a water immersion stress on them. Seven hours later, the stomachs were evulsed and filled with 10 ml of a 2 % formalin solution according to the method described in "Jap. J. Pharmac.", 18, pp. 9-18 (1968) for temporal fixation. The stomachs were incised to find the sum of lengths of ulcerated regions on the stomach bodies - an ulcer factor. A solution of 20 mg/kg of the instant compound dissolved in physiological saline was orally administered to the animals 10 minutes before stress loading.

As reported in Table 1, the instant compound showed an inhibitory action upon the ulceration of the stomach bodies.

Table 1

	Number of animals	Ulcer Factor
Control Group	10	14.8 2.0
Compound A	10	11.5 1.5
B	10	10.6 1.2
C	10	12.2 2.6
Sorbinil	10	12.6 1.8

Pharmacological Test Example 2

Effects on Treating Dermal Ulcer and Frostbite

S.D. rats weighing about 50 g (3 for each group) were used as test animals. The animals were fed with a 30 % galactose-containing powder feed. After the lapse of four weeks, their skins were grained and torn off over an area of 1 cm^2 along their back regions' median lines. At the same time, a dry ice mass of 0.5 cm^3 was bonded to each animal 2 cm below the root of the tail to get it frostbitten over an area of about 1 cm^2 at the second or third degree. The animals were subsequently fed with normal and galactose feeds to examine the influence of the accumulation of galactitol upon dermatoplasty.

The frostbitten regions were all applied with a procaine penicillin G liquid to protect them against

bacterial infection, etc. The test group of animals was applied with an ointment according to Preparation Example (a) daily for one week after frostbiting and thereafter every two days. After slaughter,the frostbitten regions were observed as to their cure degree.

The cure degree was estimated in terms of the following ranks:

+ + + : the wounds were all well-cured.
+ + : most of the wounds were cured.
+ : the wounds did not get worse.
- : at least one of the wounds got worse.

How much the animal was frostbitten was estimated in terms of the following degrees:

Second degree: erosion with broken blisters
Third degree : browning of the tissue
Fourth degree: wound reaching the bone

The cure degree of frostbite was estimated by comparing the dermal strength of the wounds with an average strength of the control group. Referring to the second degree cases of frostbite, on the one hand, + + + indicates that all the test animals attain superiority over the control animals and + + indicates that most of the test animals attains superiority over the control animals. Referring to the third degree cases of frostbite, on the other hand, + indicates that the wounds did not get worse, although they were similar in degree to those of the control group and - indicates that at least one of the wounds got worse.

A) Cure Degree of Wound (Dermal Ulcer)

Set out in Tables 2 and 3 are the results, from which it is found that the in vivo accumulation of galactitol does not only give rise to a difference in the cure degree of frostbite but has an adverse influence on dermatoplasty, and that the aldose reductase inhibitor can remarkably accelerate dermatoplasty on wounds.

Table 2 (Cure Degree of Wound)

Normally fed rats	
(1) Untreated	++
(2) Treated with ointment	+++
Rats continuously fed with galactose	
(3) Untreated	-
(4) Treated with ointment	++
Rats which were fed with galactose and normal feed after being wounded	
(5) Untreated	-
(6) Treated with ointment	+

Table 3 (Cure Degree of Frostbite)

	Degree of Frostbite	Cure Degree
Normally fed rats		
(1) Untreated	2	control
(2) Treated with ointment	2	+++
Galactose-fed rats		
(3) Untreated	3	-
(4) Treated with ointment	3	++
Rats which were fed with galactose and normal feed after being frostbitten		
(5) Untreated	3	-
(6) Treated with ointment	3	+

Use Example 1

The instant Example was carried out by having 8 volunteers use the cream preparation (c) optionally, who suffered from urtication, paralysis and xeroderma at their limbs in cold weather. One month later, questionnairing was conducted on whether the conditions got better or worse. The results are as follows.

Better	7
Stayed the same	1
Worse	0

Use Example 2

One (1) g of Compound A was dissolved in 100 ml of physiological saline with cyclodextrin to obtain a cough preparation.

The instant Example was carried out by having three volunteers drink this preparation, who then suffered coughing and inflamed throats. Later, questionnairing was conducted on whether the conditions got better or worse about the following four points. The results are set out below.

	Better	Stayed the same	Worse
a) Pain in the throat	3	0	0
b) Feeling thirsty	3	0	0
c) Chapping on the lip	2	1	0
d) Swelling and pain in the mouth and the gum	1	2	0

Claims

1. A therapeutic composition for use in the treatment of ulcers, which contains as an active ingredient a compound having an aldose reductase inhibitory activity and an ability to accelerate dermal metabolism.

2. A therapeutic composition as claimed in Claim 1 for use in treating dermal ulcers and which is in a form suitable for external administration.

3. A therapeutic composition as claimed in Claim 2 in which the dermal ulcers are corrosive wounds, bed sores, burns and frostbite.

4. A therapeutic composition as claimed in Claim 1 for use in treating labial ulcers and which is in the form of a gel liquid, ointment or cream.

5. A therapeutic composition as claimed in Claim 1 for use in treating oral and gastrointestinal tract ulcers and which is in a form suitable for internal administration.

6. A therapeutic composition as claimed in Claim 1 and for use in treating scleroderma.

7. A therapeutic composition as claimed in any preceding Claim, wherein the compound having an aldose reductase inhibitory activity is selected from d-6-fluoro-2,3-dihydro-2',5'-dioxo-spiro [4H-1-benzopyran-4,4'-imidazolidine]-2-carboxyamide, d-2-chloromethyl-6-fluoro-2,3-dihydro-spiro [4H-1-benzopyran-4,4'-imidazolidine]-2',5'-dione, and d-2-bromomethyl-6-fluoro-2,3-dihydro-spiro [4H-1-benzopyran-4,4'-imidazolidine]-2',5'-dione.

8. The use of a compound having an aldose reductase inhibitory activity in the manufacture of a medicament for the treatment of dermal, labial, intra-oral and gastro-intestinal tract ulcers, corrosive wounds, bed sores, burns, frost-bite and scleroderma.

9. Use as claimed in claim 8, in which the medicament is an optically active hydantoin compound.